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| 09/483,337 | 01/14/2000 | Eric T. Kool | 220.00040101 | 8254 |
| 26813 | 7590 | 02/14/2005 | EXAMINER | |
| MUETING, RAASCH & GEBHARDT, P.A. | | | CRANE, LAWRENCE E | |
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| MINNEAPOLIS, MN 55458 | | | PAPER NUMBER | |

1623

DATE MAILED: 02/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--------------------------------------|--------------------------------------|--|
| Office Action Summary | Application No. 09/483,337 | Applicant(s) KOOL, ERIC T. | |
| | Examiner L. E. Crane | Art Unit 1623 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2004 (amdt).
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44-48,50-54,56-60 and 64-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-48,50-54,56-60 and 64-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>09/21/2004</u> . | 6) <input type="checkbox"/> Other: _____ |

No claims have been cancelled, claims **70 and 72** have been amended, new claims **73-80** have been added, Figure 4A has been amended, and the written disclosure has not been amended as per the amendment filed September 21, 2004. One additional Supplemental Information Disclosure Statement (IDS) filed September 21, 2004 has been received with copies of all cited references and made of record.

Claims **44-48, 50-54, 56-60 and 64-80** remain in the case.

The disclosure is objected to because of the following informalities:

Incorporation by reference of essential material by reference to a foreign application or a foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by applicant, or a practitioner representing applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCAP 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In each of the above cases, the incorporations are of the complete document, and fails to properly point out the particular portions of the US patent(s) being incorporated; see MPEP §608.01(p)(1)(A) noting *In re de Seversky* and in the same paragraph (column 2 of p. 600-769, August 2001 edition) the instruction which reads as follows: “[p]articular attention should be directed to specific portions of the referenced document wherein the subject matter being incorporated may be found.”

In addition, each of the above incorporations represents a failure to provide specific disclosure of how to make and/or use. Therefore, the above citations of the *Hawkins* decisions continue to apply to all incorporations by reference.

The attempt to incorporate subject matter into this application by reference to “all patents publications and electronic publications at page 61, lines 13-15,” is improper because applicant has thus far failed to provide the requisite declarations and amendments wherein essential subject matter has been incorporated from any other reference. In order to make this

requirement clear, applicant should also be prepared to provide incorporated amendments for all US patents and applications, except for applications wherein the benefit of priority has been claimed, as well. Alternatively, applicant may elect to delete the noted sentence.

Appropriate correction is required.

Applicant's arguments filed September 21, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant argues that "Examiner has not specified what material is considered to be essential." Examiner's view of what is essential or not essential is beside the point. Applicant has asserted the right to incorporate by reference subject matter from other documents. Aside from the portion of the disclosure devoted to Background wherein incorporation by reference is unlimited, the *Hawkins* decisions are an appropriate guide for applicant to follow when determining what portions of the cited references need to be incorporated to properly describe and enable in instant subject matter. Because applicant has failed to follow the guidance of *Hawkins* and *de Seversky*, the above objection has been maintained.

The following grounds of rejection are all new and therefore no response to applicant's arguments is appropriate until otherwise noted.

Claims **44-48, 50-54, 56-60 and 64-80** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims have not met the written description requirement because the disclosure has failed to note the criticality of temperature in the execution of the autoligation process. See Northwestern University '699 (PTO-1449 ref. AM) at pages 23-25 ("Ligation Experiments") wherein the experimental conditions found to be effective for autoligation when the termini undergoing autoligation are "directly adjacent" include temperature as a critical variable when the associated hybridization process is being relied upon to distinguish between matched and mismatched hybridization outcomes, an essential part of the instant claimed detection process.

Secondly, examiner suggests that the instant claimed process wherein three probes are present is closely analogous to a combination of the “matched” and “mismatched” examples disclosed by the ‘699 reference, but fails to disclose how this variation produces a different result. In addition, the instant description fails to disclose the advantages of conducting the three probe process or how the results may be interpreted based on how the particular probes and their labels are selected.

And thirdly, examiner notes that Lehninger (PTO-892 ref. U) discloses how enzymatic ligations occur including the possibility of directly adjacent ligations and ligations which produce hairpins, but that execution of the “hairpin” alternatives has not been addressed by the instant disclosure or by the prior art of record. This is a serious fault because hairpin formation in the absence of an enzyme according to the present process claims is the necessary result of either a 1 or 2 nucleotide overlap or a 1 or 2 nucleotide gap situation. The absence of claim limitations directed to the three listed practical considerations, one of which (hybridization temperature) is deemed to be critical, suggests to examiner that applicant did not have possession of the instant claimed subject matter at the date of filing.

Claims **44-48, 50-54, 56-60 and 64-80** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of “undue experimentation” is appropriate are as follows:

A. The breadth of the claims is deemed to be excessive because the instant disclosure fails to provide an enabling description of how autoligation can be carried out when the resultant hybridization must produce a product with a hairpin (gap or overlap of the probes). In addition, the disclosure fails to explain how the desired result may be obtained without careful consideration of the temperature at which the process is conducted, a critical variable based on a careful reading of the ‘699 reference at pages 23-25 (“Ligation Experiments). Also there are no disclosures in the claims directed to the particular process conditions required to effect

concomitant autoligation with hairpin formation, a necessity associated with the presence of either a gap between, or an overlap of, the termini of the two probes which have successfully hybridized with the target oligonucleotide. And there is no disclosure of the conditions required to achieve the claimed utility of the hybridization when one probe is, as specified in claim 50, "less than 7 nucleotide in length," a variation on the prior art which is unknown when the ligation process is not enzymatic.

B. The nature of the invention: The instant claims are directed to a detection process wherein hybridization precedes an autoligation wherein either two or three autoligation-capable oligonucleotide probes bind to a target which is an optionally solid-supported linked oligonucleotide. One of the probes is always present and will hybridize with an unmutated (conserved) part of the target sequence. The second and optional third probes are complementary either to the mutated, or to the wild-type (unmutated), remaining (polymorphic) part of the target sequence, respectively. A further limitation is that the target gene mutation is not present at the junction of the autoligating probes. The autoligation process is also claimed to occur when there is i) an overlap of 1 or 2 nucleotide units, ii) when there is a gap of 1 or 2 nucleotide units between the ends of the hybridized probes or lastly iii) when there is no gap between the ends of the oligonucleotide probes, an important detail because of the physical necessity of hairpin formation as a result of successful autoligation in these cases. And the final step in the process is "detecting the presence of the autoligated oligonucleotide product," but there is no disclosure in the independent claims concerning how this detection is to be accomplished. And there is no disclosure in the claims of how detection is accomplished when, in the case of the "three probe" process claims, there is the possibility of two different autoligation products and mixtures thereof. And finally, the instant disclosure and claims suggest that ultra short probes (less than 7 nucleotides in length) are also applicable in the instant hybridization process.

C. The state of the prior art is well defined by the references of record and makes clear that the directly adjacent autoligation based testing protocol is well known in the art, but that the overlap/gap based autoligation testing protocol is unknown in the prior art. And, based on the prior art of record, there is no teaching in the prior art of autoligation as having been successfully applied with probes of less than 7 nucleotides in length as part of a single base mutant-sensitive, hybridization-based test protocol.

D. The level of one of ordinary skill is high with regard to the directly adjacent autoligation as a part of polymorphism detection as described in Northwestern University '699, but very low in the case of either overlap, gap autoligation and/or short (< 7 nucleotides) probe based hybridization processes or the application of the any of said processes to the detection of a single letter genetic polymorphism.

E. The level of predictability in the art is very high when the subject matter is limited to autoligation of directly adjacent probes hybridized to the same target oligonucleotide, but is very low when the subject matter is overlapping probes, probes with a gap, and/or with probes of less than 7 nucleotides in length are the subject matter. This low predictability is a reflection of the fact that autoligation in such situations is not known in non-enzymatic processes, presumably because the resultant product must include in the first two cases a hairpin in its structure and in the final case hybridization under high stringency conditions.

F. The amount of direction provided by the inventor is very high when directly adjacent probes undergo autoligation, but non-existent when the adjacent probes are separated by a gap or overlap one another, or when the probes are less than 7 nucleotides in length.

G. The existence of working examples: Following a careful inspection of the disclosure and particularly of the Figures, the working examples appear to be limited to directly adjacent autoligation examples and that there are no examples to enable autoligation of two probes with a gap, autoligation with two probes with an overlap, or autoligation with a probe of less than 7 nucleotide units under low stringency hybridization conditions.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be minimal with regard to directly adjacent autoligations, but excessive and therefore undue when the abutting target-sequence-hybridized probes have either a gap separating them, are overlapping, and/or are less than 7 nucleotides in length in light of the absence of examples. Examiner notes that the Lehninger et al. '613 reference does disclose hairpin containing oligonucleotides undergoing autoligation (see Figure 6), but that unlike the instant case the hairpins are formed prior to autoligation, not as a consequence of the autoligation as claimed herein. Similarly Examiner finds that the autoligations of Figures 9 and 14 in the '613 patent are also not relevant to the instant claimed processes.

Claims **44-48, 50-54, 56-60 and 64-80** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims **44-48, 50-54, 56-60 and 64-80** are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP §2172.01. The omitted element is the criticality of the temperature of the process. See Northwestern University '699 at pages 23-25 ("Ligation Experiments").

Claims **44-48, 50-54, 56-60 and 64-80** are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP §2172.01. The omitted step(s) are the experimental variation(s) required to insure that autoligation occurs when there is either a gap of 1 or 2 nucleotide units or an overlap of 1 or 2 nucleotide units.

In claim **44** at line 13, and in claim **65** the term "not directly adjacent to" is indefinite because said term has not been defined in the disclosure. In applicant's response at page 29 the term "not directly adjacent to" has been defined, but examiner could not find any corresponding definition in the disclosure, with particular attention paid to the vicinity of page 16.

The process of claim **50** is unclear and or incompletely defined because the instant process has not provided a clear description of how a minimum of two different possible products, or the mixture of the two or more different products, are separately detected. For example, the "target polynucleotide" may be homogeneous or a mixture of multiple different sequences, and therefore capable of generating multiple different products. There is no step describing either how the different products are distinguishable, how to detect either product, or how to detect mixtures of products. In addition, there is no indication within the claim as to how the process avoids "probe dimers," that is products which occur following either self or cross hybridization of the two different probes specified, a particular difficulty when hybridization under low stringency is applied. The need to specify stringency is also important when referring to the hybridization of the "universal oligonucleotide probe" because, as noted in the **Sommer et al.** reference, (PTO-892 ref. S), the conditions applied have a major impact

on how faithful the hybridization takes place in practice, a limitation which is incompletely described by the term “binding” (claim 50 at line 9) in the noted claims.

In claim 50 at lines 7 and 10, the term “analogous” is indefinite for failure to specify either the degree of homology and/or complementarity or whether the term which occurs twice in line 7 has the same meaning at all three noted locations.

In claims 44 and 50 the term “close proximity to one another” is indefinite for failure to define the distance. Examiner notes in Biochemistry, 2nd Ed., by Lehninger at page 898-899 (PTO-892 ref. U) the description of nick translation, and that the this process can work to rejoin the termini by i) rejoinder with hairpin formation, or ii) introduction of the missing bases in sequence or in seriatum with a polymerase enzyme effecting re-establishment of the missing bonds in the deoxyribophosphate backbone. The instant claims are incomplete because they fail to indicate with reasonable specificity the conditions which must be applied to effect bond formation by autoligation when formation of a hairpin is required and how these conditions differ from the conditions of autoligation when there is neither a gap nor an overlap (e.g. “directly adjacent” as in Northwestern University ‘699).

Claims 44 and 50 are incomplete because there is no clear description of how the claimed test result (“detecting a genetic polymorphism”) is actually realized at the end of the claim. The term “detecting the presence of the autoligated oligonucleotide product” is only functional language. See also claims 56, 64-73 and 78-80. Claim 45 does not overcome this rejection because the limitation therein is not found in the independent claim 44. See also claims 56 and 57. Claim 51 does not overcome this rejection because, with three probes present, there must be at least two different probes labeled differently in order to determine the identity of all of the possible product(s) generated using tests for the presence of said labels. See also claims 73 and 74.

In the preamble to claims 44-45, 47-48, 50-51, 53-54, 56-57, 59-60, 64-74 and 76-80 the term “polymorphism” suggests that the test is directed to finding -- mutations --. The noted term reappears later in each of the listed claims as part of the terms “genetic polymorphism,” “mutant polymorphism” and “wild type polymorphism” suggesting two or more different and conflicting meanings for the originally noted term. The question implied by the noted term but not answered is: “Is the claimed test protocol directed to finding the wild-type polymorphism,

the mutant-type polymorphism, or as the claims appear to imply must both polymorphisms be present in the same sample?" Examiner has included a second reference to King's Dictionary of Genetics including page 307 wherein a definition of "polymorphism" is presented. Applicant is respectfully requested to amend the claims to address this inconsistency of meaning and the confusion which results therefrom.

The following rejection has been repeated and therefore applicant's arguments are responded to following this rejection.

Claims **44-48, 50-54, 56-60 and 64-80** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **44, 50 and 56** at lines 8, 9 and 10, lines 12, 14, 17, 18, 19 and 20 and lines 7, 8 and 9, respectively, the term "comprising" renders the metes and bounds of the claim indefinite, particularly because said term refers to chemically modified starting materials and products and by such reference implies the absence of a complete description of the structural features of said chemically modified starting materials and products. Said term, as a synonym of including, begs the question -- Including what else?-- See also claims **64-73 and 78-80** wherein the all except the first occurrence of the term "comprising" render each of the noted claims indefinite.

Applicant's arguments filed September 21, 2004 have been fully considered but they are not deemed to be persuasive.

Applicant argues that previous cases issued by instant examiner and other examiners have relied on the term "comprising" as a judicially recognized term of art. Examiner agrees in part, but notes that instant examiner routinely rejects claims as herein when the term comprising is directed to the structures of chemical compounds for the reasons noted.

Applicant subsequently argues that the term "comprising" in the noted locations "is clear and informs the public of the boundaries of what constitutes infringement of the patent." Examiner respectfully disagrees and notes that applicant's argument is conclusory and ignores the points made in the rejection of record. Examiner notes applicant's quotation of the MPEP and responds as follows: it is unreasonable from examiner's point of view to not enforce the

statute which in this case requires reasonably defined metes and bounds of the claimed subject matter. As noted in the rejection the term "comprising" implies that there is subject matter of a chemical structural nature which is not defined in the claim. In light of the fact that applicant can substitute the terms like "having the structure" and include the structure, or substitute for "comprising" narrow language like -- consisting of --, examiner renews and repeats the above rejection and the response to argument from the previous Office action as follows.

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive.

Applicant alleges that the above rejection is not understood because "it is not clear as to which part of the claim the Examiner is applying the rejection." Examiner has amended the rejection to more particularly point out why the rejection was made, more particularly point out the term to which it is deemed to apply, and the lines in which said term appears in the noted claims. Applicant also argues that "comprising" is an acceptable transitional term. Examiner agrees in part, but in rebuttal argues that this term does not apply to claims or portions of claims directed to chemical structures because said term may be read to imply an incomplete description of the chemical structure; e.g. the claim -- A compound comprising ethanol. -- reads on potable distilled liquors and/or on chemical analogues of ethanol whereas the claim -- A compound having the formula $\text{CH}_3\text{-CH}_2\text{-OH}$. -- is directed only to the compound ethanol and may not be read to include mixtures of ethanol with other substances or to compounds which are structurally related to ethanol.

The following grounds of rejection are all new and therefore no response to applicant's arguments is appropriate.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent."

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

(e) the invention was described in a patent granted on an application to another filed in the United States before the invention thereof by applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent."

Claims **56-60 and 70-72** are rejected under 35 U.S.C. §102(e) as being anticipated by **Lehninger et al '613** (PTO-1449 ref. AF).

Applicant is directed to the process outlined by Figure 1 and to column 1 lines 13-28 wherein the instant claimed process claims have been anticipated when the ligation is between probe termini which are a 3'-phosphorothioate and a 5'-leaving-group-modified carbon and wherein said termini are "directly adjacent." See column 4 at lines 40-67 wherein the leaving group is defined to include a 5'-deoxy-5'-iodonucleotide at the 5'-terminal position of one of the autoligating oligonucleotides. While the instant reference does not use the terms "mutant polymorphism oligonucleotide probe," "universal oligonucleotide probe," and "target polynucleotide," the three components of Figure 1 of the '613 patent which correspond are readily identifiable as the "3'-modified oligonucleotide," the "5'-modified oligonucleotide," and the "template oligonucleotide," respectively. The difference between the terms "oligonucleotide" and "polynucleotide" is not deemed to be a proper basis for distinguishing the reference because the instant claims do not define the term "target polynucleotide" to exclude 16-mers which Figure 1 of the reference define as "oligonucleotides."

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims **56-60 and 70-72** are rejected under 35 U.S.C. §103(a) as being unpatentable over **Lehninger et al. '943** (PTO-1449 ref. AC) in view of **Lehninger et al '613** (PTO-1449 ref. AF) and further in view of **Gryaznov et al. '903** (PTO-1449 AB).

The instant claims are directed to testing for the presence of a mutation (polymorphism) in a target polynucleotide by contacting same with two probes one of which ("mutant polymorphism probe") and the other is a probe which hybridizes with a portion of the target

immediately adjacent to the portion which hybridizes with the first probe. As the name suggests, the first probe hybridizes with the part of the target wherein the mutation occurs. The method of testing is effected by the concomitant hybridization of the two non-target probes with the target nucleic acid and, because of the presence of 3'-phosphorothioate and 5'-leaving group chemical modifications of the two probe sequences, spontaneous ligation occurs to give a longer probe hybridized to the target nucleic acid. No particular method of detection of the final hybrid's presence is not specified in the claim.

Lehninger et al. '943 discloses at columns 9-11 and Figures 6A-6F a method of detecting the presence of a mutation by concomitant hybridization by two probes with a target nucleic acid including spontaneous autoligation, with ultimate detection by high performance liquid chromatography and/or other chromatographic methods.

Lehninger et al. '943 does not expressly disclose the particular 5'-terminal modification relied on by the instant claims or all of the 3'-modifications specified by the instant claims.

Lehninger et al. '613 discloses at column 4, lines 40-67, that the 5'-modification may include a 5'-deoxy-5'-iodonucleotide terminus and that this modification is specifically taught to be an alternative to that of the '943 process at column 5, lines 25-36 of this reference.

Gryaznov et al. '903 discloses at column 3 at lines 50-56 that autoligating probes of the kind claimed herein may be modified at their 3'-termini by the introduction of phosphorothioate or a phosphoroselenoate among 6 alternatives to phosphate.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the process of the '943 reference according to the '613 reference by substitution of the terminal modifications of the '613 reference because this possibility is specifically taught in the '613 reference.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the '943 process according to the '903 disclosure by substitution of phosphoroselenoate for phosphorothioate because both the '943 and the '903 references are both directed to hybridization processes wherein autoligation between 3'-modified and 5'-modified probes is part of each disclosure. In addition, the '943 reference references numerous alternative autoligation coupling methods beginning in the paragraph bridging columns 2-3. A

similar disclosure is made in the '903 reference in column 6 at lines 32-50. These teaching are deemed to have motivated the ordinary practitioner seeking to optimize the prior art process to look for alternatives to guide the process of optimization. [

One having ordinary skill in the art would have been motivated to combine these references because the '943 reference noted above clearly teach a basis for the combination of the first two references. The combination of the first and third references is also well motivated because of the overlapping subject matter and the other reasons noted above.

Therefore, the instant claimed method of testing would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Claims **44-48, 50-54, 64-69 and 73-80** would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. 112.

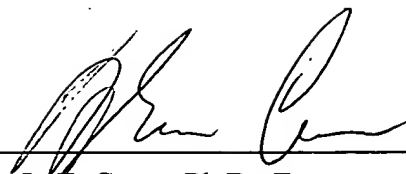
Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 703-872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
02/11/2005

A handwritten signature in black ink, appearing to read 'L. E. Crane', is written over a horizontal line.

L. E. Crane, Ph.D., Esq.

Patent Examiner

Technology Center 1600